REMARKS

The Office Action of June 16, 2004 has been reviewed and its contents carefully noted. Reconsideration of this case, as amended, is respectfully requested. Applicants thank the Examiner for her thorough and detailed remarks. Claims 19, 21 and 25-27 29-30, and 34-38 are currently pending. Claims 19, 21, 25, 29 and 30 are amended herein. Claim 23 is again canceled herein, as are claims 22 and 28. Claims 34-38 have been added herein.

Clarification as to Claim 23 and Entrance of the Amendment

Applicants note at the outset that in the Examiner's action of June 16, 2004 the Examiner states that claim 23 remains pending. Respectfully, Applicants wish to clarify that they canceled this claim in the last action of March 10, 2004. From the comments provided by the Examiner it appears that the entire amendment of March 10, 2004 was entered, but that the appropriate notations for claim 23's cancellation were not made. (See Office Action Summary – Disposition of Claims, Detailed Action – page 2 of Office Action.) Clarification is respectfully requested. Applicant will proceed under the assumption that the Amendment of March 10, 2004 was entered. Applicant also notes that the cancellation notation for claim 23 was left in the presentation of the claims above.

Acceptance of Drawings

Applicants thank the Examiner for accepting the January 23, 1998 drawings.

New Matter Rejection

Examiner rejected claims 29-30 are rejected under the first paragraph of 35 USC § 112 relative to inability to comply with the written description requirements.

In response Applicants have made amendments to the claims without prejudice which they believe render moot the Examiner's new grounds of rejection. Applicant, however, respectfully

retains that right to re-assert separate claims for physiologically active immunoglobulin fragments in a separate application.

The Rejections Under 35 U.S.C. §103(a)

Meade et al., and DeBoer et al.,

Claims 19, 22 and 25-28 remain rejected under 35 U.S.C. §103(a) as being unpatentable over the Meade et al., reference (U.S. Patent No.# 4,873,316)(hereinafter the '316 patent) and the DeBoer et al., citation (U.S. Patent No.# 5,633,076)(hereinafter the '076 patent). The rejection of the claims, as amended, is respectfully traversed.

Applicant points first to the amended claims that were so modified to bring further away from the teachings of prior art citations Meade et al., and De Boer et al. Applicant also maintains, respectfully, that the Examiner has failed to establishment the required *prima facie* case of obviousness. Therefore, in light of previously presented arguments and without more, the claims are not rendered obvious and should go to issue. In re Oetiker, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir.1992).

It is important to point out that there is no requirement in patent law that the a patentable product be produced by non-obvious or novel methods, regardless of whether that product is a DNA construct, or an amino acid sequence but only that the product itself be non-obvious. In re Bell, 26 USPQ2d 1529 (Fed. Cir. 1993); In re Thorpe, 777 F.2d 695, 697, 227 USPQ 964, 966 (Fed. Cir. 1985). As an example, the Federal Circuit upheld this principle in *In re Bell* where the court found that the genes for human insulin like growth factors I and II (IGF) were not rendered obvious by the previously disclosed full amino acid sequences, even narrower than the Examiner's concern here. There have been no similar products to those claimed by the applicant. Bell.

In determining obviousness, the basic issue is whether applied references, alone or in any combination, suggest the claimed invention as a solution to the specific problem solved. When the prior art itself does not suggest or render obvious the claimed solution to that problem, the art involved simply does not satisfy the criteria of 35 U.S.C. § 103 for precluding patentability. Obviousness cannot be established by combining the teachings of the prior art to produce the

claimed invention, absent some teaching, suggestion, or incentive supporting the combination. Carela v. Starlight Archery, 231 U.S.P.Q. 644 (Fed. Cir. 1986).

The critical inquiry in combining various prior art references is whether there is some reason or motivation to combine present in the prior art as a whole that would motivate a person of ordinary skill in the art to combine those references. Pro-Mold & Tool Co., Inc. v. Great Lake Plastics, Inc., 75 F.3d 1568, at 1573 (Fed. Cir. 1996). When the party challenging patentability relies upon a combination of prior art to so establish, then that party then bears the burden of showing some teaching or suggestion in the references for the combination. Ashland Oil Inc., v. Delta Resins & Refractories, Inc., 776 F.2d 281 (Fed. Cir. 1985). As a Federal Circuit court stated over a decade ago:

> "It is insufficient that the prior art disclosed the components of the patented device, either separately or used in other combinations; there must be some teaching, suggestion, or incentive the make the combination made by the inventor." Northern Telecom Inc., v. Datapoint Corp., 121 F.2d 931, 934 (Fed. Cir. 1990). In this sense it is improper to the Applicant's ideas as a instruction manual on reconstituting the prior art. R. Harmon, **PATENTS AND THE FEDERAL CIRCUIT** § 4.7 (3d edit. 1994).

No such suggestions were, respectfully, made in the cited prior art and therefore the case for obviousness can be made.

Meade et al.,

As previously stated, the Meade et al, patent provides some insight and teachings in the use of DNA constructs and in the development of transgenic animals for the production of biopharmaceuticals in milk. However, the teachings of Meade et al., do not by themselves or in combination with any of the other cited art render the instant claims obvious.

The subject matter of the remaining claims is directed to DNA constructs for providing a heterologous immunoglobulin in the milk of a non-human transgenic mammal. The construct of the invention includes an appropriate promoter sequence that results in the preferential expression of a protein-coding sequence in mammary gland epithelial cells, an immunoglobulin protein-coding sequence, a 3' non-coding sequence; and a unique restriction site between the promoter and the 3' non-coding sequence, wherein the immunoglobulin protein-coding sequence of interest is inserted into the restriction site.

More to the point for the immediate claims is objective fact that Meade et al., patent fails to provide or teach the following:

I. Meade et al. fails to teach or suggest that expressing the light chain and heavy chain of an immunoglobulin separately by using a mammary epithelial cell comprising at least two vectors, one encoding the heavy chain and one encoding the light chain. Meade et al., simply fails to contemplate expressing these chains separately;

II. Meade et al., fails to teach a separate construct for the light chain and the heavy chain for the production of a single immunoglobulin species;

III. Meade et al, fails to indicate that the use of two separate vectors can result in a cell capable of producing an assembled, functional immunoglobulin in milk;

IV. Meade et al., fails to teach the unique construction of the restriction site – such that it has a coding sequence inserted into the site- that then allows for a vector which can easily be modified, without the need for cleaving the remaining construct to insert various immunoglobulin chains is an improvement over the prior art. This construction allows for easier expression of a variety of different immunoglobulin coding sequences. Thus, the use a unique restriction site into which the immunoglobulin coding sequence is inserted, adapts to the unique features of expressing immunoglobulins.

As can be seen from the amended claims, each of the above elements provided are integrated into the pending claims. Given this, and the controlling precedent cited above, the cited are simply fails to render the instant invention obvious. Reconsideration of the rejected claims is respectfully requested.

DeBoer et al,

DeBoer et al., does not provide what Meade lacks, see "I" through "IV" above. Importantly, neither Meade et al. nor DeBoer et al. teach or suggest the claimed construct having a unique restriction site in between the promoter and the 3' untranslated region into which an immunoglobulin protein-encoding sequence is inserted. DeBoer also fails with regard to each and every other element called out above as deficient in Meade et al. Respectfully, the lack of even one element I – IV as provided above is sufficient to prevent an obviousness rejection from being maintained.

Respectfully, and to clarify the Applicants position DeBoer et al. does not make up for any of the other deficiencies of the Meade et al. reference. Specifically, the Applicants understand the assertion of the Examiner that DeBoer et al., at Column 30 lines 45-50 and Figure 7E provides for the development of a construct having a casein promoter and a 3' non-coding sequence, and unique restriction sites, including XhoI, between the promoter and the 3' coding sequence. Applicants again state , however, that neither the textual citation of DeBoer or the Figure relied upon by the Examiner demonstrates a mammary gland specific promoter and a 3' non-coding region wherein there is a unique restriction site into which an immunoglobulin-coding sequence has been inserted. Therefore, this citation simply does not present the elements of the current invention regarding the production fully-functional, fully-assembled immunoglobulins in transgenic mammalian milk. It does not attempt to teach this modification of the prior art. Moreover, it does not teach any combination with Meade et al.

Thus, amended independent claim 19, which recites elements not rendered obvious by Meade or DeBoer alone or in combination, cannot be obvious as against either of these references. Therefore, the Examiner's rejections are traversed and reconsideration is respectfully requested. Reconsideration is respectfully requested.

Dependent claims 25-27 and 30 being dependent upon and further limiting independent amended claim 19 should also be allowable for those reasons, as well as for the additional recitations they contain. Applicants respectfully request reconsideration of the rejection of claims 19, and 25-28 under 35 U.S.C. § 103(a) in view of the above amendments and remarks.

The new claims 34-38 provided herein should be allowable for the recitations that they contain, and in light of the arguments made previously.

Vandamme et al.,

Amended claims 29 and 30 remain rejected under 35 U.S.C. §103(a) as being unpatentable over the Meade et al., DeBoer et al., references in view of Vandamme et al. This rejection is, respectfully, improper, and should be reversed.

The limitations of the DeBoer et al., and Meade et al., citations are provided above. Moreover, with regard to claims 29 and 30 the Examiner notes that these citations "do not teach a mammary gland epithelial cell comprising two separate vectors encoding the heavy chain and light chain of the immunoglobulin" (Office Action of 12/17/02 page 5, 2nd paragraph). In addition, they do not add "expressing such chains separately...concomitantly."

Vandame et al., does not and cannot make-up for these deficiencies. Moreover, the newest citations again limit Vandamme's usefulness in any combination in the effort to prove the amended claims obvious.

Morevoer, and as stated previously Applicant must again respectfully point out that the Examiner does not provide any support to support her suggestion that the Vandamme *et al.*, an *in vitro* cell culture system, could in any manner, fashion or design serve as an accurate approximation of functional mammary gland in a whole animal, and therefore would not lend itself to the creative capabilities of the ordinary worker in the field.

The mammary organ is an exceptionally complex tissue that produces a very complex mixture known as milk. This process is initiated only in mammary epithelial cells in response to a specific order and cascade of hormones within the adult female mammal. The instant invention provides for using that process through the manipulation of various cell populations to produce a fully-assembled, fully-functional immunoglobulin of exogenous origin not otherwise found in milk.

In fact, any teaching that proposes the use of *in vitro* expression methods as optimal is in essence teaching away from the whole animal transgenic model & platform of the Applicants. Thus, in addition to being non-analogous art any teachings to those in the field would be to teach away from the approach reached by Applicants. Therefore, the Examiner's analysis thus inappropriately bases its rejection on the use of Vandamme et al., on the premise that one expression system and all of the interplay in the various tools used to achieve expression of a target

protein or protein fragment is much like another, and that therefore any cellular expression system with any given target protein is an appropriate and analogous prior art reference for the claimed invention of another such expression system.

It must again be pointed out that the Vandamme reference is objectively deficient with regard to:

a. whole animal systems;

b. the physiological effect of lactation hormones;

c. milk promoters; and

d. comparative *in vivo* expression systems.

These fundamental differences are simply not overcome and lead to a movement away from a transgenic based system towards a cell culture based system. That is, Vandamme is non-analagous art. The problems are different as are the solutions. More important, no one in the prior art established an *in vitro* system where the efficiency of synthesis of milk component proteins, including exogenous immunoglobulins of interest, even approximate those found *in vivo*. Whole animal experiments involve the incredibly complex web of physiologic interactions never even approximated by cell culture research. Prolactin, insulin and hydrocortisone are the minimal hormone mix needed to induce mammary cell differentiation and cause inactive cells to become active, but use of them in a vacuum as in the isolated culture dish does not and cannot approximate the effects on an whole animal. Thus, there is no *in vitro* system to study regulation of milk synthesis in active cells. The claims relate to established lactation in a whole animal and demonstrate elevated milk protein synthesis in the whole animal. More to the point Vandamme is simply not available for combination with any whole animal transgenic system of the type provided by Applicants and there is not and cannot be any suggestion to combine.

Given the above, no obviousness rejection can be maintained based on the Vandamme *et al.*, reference. Therefore, any rejections of the claims at issue here under § 103 based in whole or in part on Vandamme should be reversed, and such is respectfully requested.

Other than a fee for the appropriate extension of time no fee is deemed necessary in connection with the filing of this Amendment. However, the Commissioner is authorized to

charge any fee which may now or hereafter be due for this application to GTC Biotherapeutics' Deposit Account No. 502092.

Applicants respectfully submit that the pending claims of this application are in condition for allowance, and that this case is now in condition for allowance of all claims therein. Such action is thus respectfully requested. If the Examiner disagrees, or believes for any other reason that direct contact with Applicant's attorney would advance the prosecution of the case to finality, the Examiner is invited to telephone the undersigned at the number given below.

Early and favorable action is earnestly solicited.

Respectfully Submitted,

Date: 12/15/04

By: _____

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